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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/293,670 04/16/99 FISHER J A-68104/DJB/

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WESSENDORF, T	
ART UNIT	PAPER NUMBER

1618 6
DATE MAILED: 10/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/293,670

Applicant(s)
Fisher et al

Examiner
T. Wessendorf

Group Art Unit
1618



☒ Responsive to communication(s) filed on Jun 4, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-10 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-7 is/are rejected.

☒ Claim(s) 8-10 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

* *Notice to comply requirements for nucleotide sequence*

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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The oath or declaration claims priority under 35 USC 120 on copending applications Serial Nos. 09/062,330 and 09/157,748 filed 4/17/98 and 9/21/98, respectively. However, applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78) following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The drawings are objected to because of the reasons set forth in PTO 948. Correction is required.

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Also, the specification at page 6, line 15 describes Figures IA, IB and IC. However, Figure 1 of the drawings does not show or label Fig. 1 as figures 1A-1C.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

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Timing of Corrections.

Applicants are required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible.

The disclosure is objected to because of the following informalities:

A). There are no Seq. ID. Nos. for the different peptide sequences recited e.g., at page 15, lines 16-20; page 22, lines 26 and 28; page 23, line 10. Applicants are requested to check for other sequences in the specification since they are too numerous to mention specifically. Furthermore, these sequences do not comply with the requirements set forth under 37 C.F.R. 1.821-1.825. See attachment.

B). Syntax errors, examples of these errors are: "thorough" at page 9, line 28 (should be --through--); "colonrectal" at page 10, line 22 (should be two words); "reporta" at page 44, line 14 (should be two words); "with with" at page 46, line 13.

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The specification has not been checked to the extent necessary to determine the presence of **all** possible minor errors (grammatical, typographical and idiomatic). Applicants' cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The use of the trademark e.g., CELLTRACKER at page 13, lines 10 and 14-15 or tradename "HOECHST" at e.g., page 13, line 24 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the p21 as the bioactive agent for a particular cell population such as the tumor cells, does not reasonably provide enablement for a library of bioactive agents or nucleic acid that encodes said bioactive agents and a population of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enablement provided in the specification is not commensurate in scope with the recited method employing the broadly recited library of bioactive agent or a library of nucleic acid encoding said bioactive agent and a population of cells. The specification, like the claims, merely contains broad generalized statements. However, the exemplification provided in the specification examples is drawn to a single bioactive agent, p21 for a particular type of cell population, tumor cell population. It is not apparent from the single example how the p21 has been considered a candidate for a bioactive agent since the nucleic acid encodes specifically said p21. There is no guidance or reasonable assurance in the specification that the

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method and results employed and obtained for the single bioactive agent would be predictive of similar effect to the thousands of bioactive agent of the same or different components and cell population especially when the components present in the bioactive agent or cell is unknown. It would take an undue amount of experimentation for one skilled in the art to determine the incalculable parameters included in the broadly claimed scope.

The factors that are to be considered in the determination of undue experimentation is disclosed in *In re Wands*, (U.S.P.Q. 2d 1400 (CAFC 1988)). These include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, the predictability of the art and the breadth of the claims.

1). The specification fails to give adequate direction and guidance in how to readily go about determining the bioactive agent(s) present in a library of unknown composition, whether said bioactive agents present in the library are identical or different, the number of said bioactive agents comprise in the library, the method of screening or determining as to whether a bioactive agent is a candidate for cell population reaction, the size of the library comprising the different bioactive agents,

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the altering effect of the bioactive agents on the phenotype of the cell population, the type of cell population that can be altered by a bioactive agent, the different parameters that can be measured by a change in the cell morphology and etc.

Furthermore, the specification does not provide adequate direction with regards to the library of nucleic acid encoding said bioactive agents or the expression package of the nucleic acid; where one can make insertions in an expression system so as not to cause deleterious effects on the viral vector. If the expression vector use is a viral vector, there is no direction and guidance concerning how to determine which sites will not affect the viral life cycle such as the ability of the virus to attach and enter a cell. The nucleic acid fusion libraries may contain so many inserts per viral vector that the synthesis of the inserts produces an observable effect on the host metabolisms. Because of this, there is very significant censorship of the library due to a broad set of selection factors ranging from proteins synthesis to virion assembly.

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2). Applicants have failed to provide any working examples for any library of bioactive agent or nucleic acid in any vector transfected into any organisms such as virus, yeast or bacteria.

3). The state of the prior art is such that the consequences of some bioactive agent and cell interaction on some cells have not yet been fully determined or elucidated. See Polyak (Genes and Development) at e.g., page 1945, col. 2.

4). The art is inherently unpredictable with respect to the numerous types of bioactive agent that alters a given cell population, the vectors use in nucleic acid expression or display wherein even if one surface protein is identified as a candidate bioactive agent it is not possible to predict what effect the insertion of other bioactive agent into the viral protein will have on the agent or the vector package *a priori*. Also, the use of a wide variety of libraries with bioactive agent presentations can be displayed in an extraordinarily large number of conformations. See Nakanishi (The EMBO Journal) e.g., at page 556, col. 2, last paragraph and Tournier et al (Molecular Biology of the Cell) e.g., at page 658, col. 2.

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5). The breadth of the claims encompasses a large possible combinations for the different recited variables such as the large diversity of bioactive agent or nucleic acids that encodes said bioactive agent and cell population.

6). Therefore, while the level of skill in the art is high, the molecular biology and gene art is so unpredictable that it would require undue experimentation to make the invention commensurate in scope with that claimed in the absence of adequate guidance or direction as set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in that the preamble recites for a screening for a bioactive agent but the body of the claim does not recite positive process steps of screening for said bioactive agents.

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Claims 8-10 are objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, these claims have not been further treated on the merits.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 5-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 12-33 and 35 of copending Application No. 09/062,330('330). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed method of screening for bioactive agent capable of altering a cellular phenotype and sorting said cells by FACS machine on the basis of at least five

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cellular parameters (claim 1) includes the specifically claimed parameters of the '330 application. The specific parameters are claimed in the instant claim 5. The claims in each application appear to be identical as the same method steps are claimed in each instances except the claims in the '330 have been merely multiplied to claim the individual parameters.

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of copending Application No.09/157,748 ('748). Although the conflicting claims are not identical, they are not patentably distinct from each other because the difference seen is merely in the preamble, but the method steps in each applications are the same. The instant preamble of claim 1 claims alteration in the cellular phenotype which obviously include or is a variant of the cell cycle phase claimed in the '748 application. (Note the instant claim 7 which recites said cell cycle parameter measurement). [Applicants should clearly set forth a demarcation line among these applications].

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-7 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 09/157,748 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future patenting of the conflicting application. See the provisional obviousness type double patenting, supra.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131.

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Applicants have provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as the '739 application at the time this invention was made. Accordingly, the '739 application is disqualified as prior art through 35 U.S.C. 102(f) or (g) in any rejection under 35 U.S.C. 103(a) in this application. However, this applied art additionally qualifies as prior art under subsection (e) of 35 U.S.C. 102 and accordingly is not disqualified as prior art under 35 U.S.C. 103(a).

Applicants may overcome the applied art either by a showing under 37 CFR 1.132 that the invention disclosed therein was derived from the invention of this application, and is therefore, not the invention "by another," or by antedating the applied art under 37 CFR 1.131.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

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Claims 1-4 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Noaln (WO 97/27212).

Noaln discloses a method of screening for a bioactive agent capable of altering a cellular phenotype of a cell which comprises combining at least one bioactive agent and a population of cell or introducing a library of nucleic acids encoding a candidate bioactive agents into a population of cells and sorting said cells in a FACS machine by separating said cells on the basis of at least five cellular parameters (claim 1) or at least three cellular parameters (claim 3). Note e.g., page 3, lines 6-13; page 4, lines 26-27; page 14, lines 1-22; page 18, line 30 up to page 19, line 17; page 23, line 19 up to page 24, line 6; page 28, lines 25-29; page 29, line 8 up to page 30, line 16; page 31, line 7 up to page 32, line 6; page 33, lines 19-28; page 34, line 10; Example 4, page 73 up to page 80.

The method of Noaln therefore fully meets the claimed invention.

Claim 3 is rejected under 35 U.S.C. 102(e) as being anticipated by Kamb (5,955,275).

Kamb discloses a method for identifying (i.e., screening) perturbagens (bioactive agents) that affect a cellular phenotype which comprises introducing a library of nucleic acid

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into the cells and sorting said cells by FACS machine based on at least three parameters such as reporter expression i.e., green fluorescent protein release or uptake, general effects on gene expression e.g., expression of the β integrin and/or cell viability e.g., antibody staining. Note e.g., col. 3, lines 5-53; col. 5, line 14 up to col. 8, line 63; col. 14, lines 38-52; col. 17, lines 37, lines 39; col. 20, Example 2 up to col. 22, line 61.

The method of Kamb therefore fully meets the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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Claim 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Noaln or Kamb in view of Hide et al(Jrnl. of Cell Biology).

Noaln and Kamb are discussed, above. Noaln further discloses at e.g., page 31, line 7 up to page 32, line 6 the FACS means of measuring the altered cellular phenotype except the claimed recitation that the cellular phenotype is exocytosis. Kamb similarly discloses FACS sorting of cells except for the claimed cellular phenotype is exocytosis. However, Hide discloses e.g., at page 488, col. 2 that cells (mast) contain large numbers of secretory granules which makes them highly refractile which is manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of (mast) cells. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Noaln or Kamb by exocytosis since exocytosis is one of the means of classifying cell populations as taught by Hide (and appears to be a sensitive measure of the cell behavior as shown by its high refractile

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property). Furthermore, while Kamb or Noaln does not positively recite said exocytosis as the cellular phenotype however, it is considered that the process of Kamb or Noaln is obviously an exocytosis since cellular excretion or discharge of a substance from the cell occurs as a result of fusion of membranes. Thus, the teachings of Kamb, particularly, of measuring e.g., β integrin is obviously the claimed measurement of the quantity of granule specific proteins. Furthermore, it would have been obvious to measure the cellular parameter as the recited proliferation or cell phase in view of the teachings of Kamb or Noaln as to the measurement of cell viability, a viable cell obviously is a proliferating cell that is undergoing cell phase cycle.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. Wessendorf whose telephone number is (703) 3967. The examiner can normally be reached on Mon. to Fri. from 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams, Ph.D., can be reached on (703) 308-0570. The fax phone number for this Group is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Tdw

10/1/99

T. Wendy
Patent Examiner